January 15, 2001

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Via FAX

Dear Dr. Meslin:

Thank you so much for sending us a copy of the draft of NBAC's report on Ethical and Policy Issues in Research Involving Human Participants.

We applaud the Commission for undertaking this truly Herculean task and developing a comprehensive report with detailed recommendations for reform of the human research protection system. I sense that in the annals of bioethics it will have parallel importance to the Belmont Report. The only question is whether the government, academia, and private industries will implement NBAC's recommendations

The history of tragedies associated with lapses in, or absence of human research protections in the United States is painfully clear. Your report touches on the major scandals associated with World War II Nazi atrocities, the Tuskegee experiment, Willowbrook, the Brooklyn cancer experiment, government radiation tests, etc. All of these, along with other research catastrophes, culminated in the death of Jesse Gelsinger during a 1999 gene transfer experiment, and catapulted the questions of human research protections back into the headlines. The public anxiously awaits your recommendations to once and for all prevent these tragedies from recurring. The research enterprise is losing the public's trust, and we pray that your report will spur needed reform to ensure that participants in human research experiments will be protected in the future.

The report mentions many of the major changes to the research environment in recent decades that cry out for reform. We believe the principles of the *Belmont Report* must be adhered to, but they must also be updated to address modern technologies and unique ethical problems posed by emerging new technologies.

As the report aptly notes, a great deal of clinical research no longer occurs in one institution. We sense that informed consent documents for multi-site experiments should be uniform. However, legal personnel at each institution often insist on their own specific legal wording because they are mostly concerned about liability, not about protection of research volunteers. So we suggest that the report should put more emphasis on protecting research participants in multi-site trials, and recommend very clearly that the same informed consent document should be used at all of the participating clinical sites. Perhaps only one IRB should review, approve, and monitor a multi-site trial rather than several local IRBs.

The impact of new technologies, and the unique ethical questions that they sometimes raise, should also be addressed in your recommendations. Gene therapy, cloning, fetal cell transfers, xenotransplantation, stem cell research, in utero gene transfer, genetic tests, etc., all raise new ethical questions and pose human protection problems. The human research protection system must always be prepared to respond quickly and decisively to unique ethical issues as they arise in the future. In other words, we urge you to make it clear that the system should always be prepared to act forcefully and immediately to new circumstances, and should not have to wait for an act of Congress to, for example, prohibit certain research (e.g., cloning a human being, or engineering a half animal/half human entity). If IRBs are empowered to vote against approval of these types of experiments, or to defer to a higher authority such as the NOHRO, such research should be delayed while public debate is pursued.

We also suggest that there are vast differences between biomedical and other types of research (e.g., sociological research) which are not defined separately in your report for the purpose of creating a similar but not identical oversight system. Surely the basic principles of the *Belmont Report* should be applied to all types of human research, but we suggest that different processes of protocol review and approval should be considered. The non-medical research community is crying out for separation of the review system.

It is my understanding that IRBs are currently responsible for review and monitoring of <u>all</u> human research at their institutions. Even though IRBs are primarily composed of medical members, they must review non-medical protocols such as sociology and anthropology research. This has caused great concern because there are no requirements that anthropology research protocols, for example, should be reviewed by anthropologists. Therefore, I highly recommend that IRBs which review medical research should not be responsible for non-medical research oversight. Instead, the composition of non-medical IRBs should be clearly spelled out in your report with the principle that peer-reviewed research inherently requires "peers" of the same discipline.

You propose that at least 50 percent of IRB membership should not be employees of the institution. We applaud this recommendation. However, we caution that this will be a very

difficult requirement for most institutions to meet. It may substantially delay reviews of protocols and oversight activities.

We suggest that a completely restructured human protection system might be warranted because IRBs do not have sufficient resources, nor expertise, and there is an inherent conflict-of-interest in the very fact that they are local and have an interest in the financial well-being of their institution. Countywide, statewide, regional, or national IRBs would remove this conflict-of-interest and they could be funded by county or state governments. National IRBs are currently paid by commercial sponsors. We also endorse the concept of topic-specific IRBs especially because of the new medical technologies and the broad range of diseases that are studied. No IRB can contain members who are expert on so many new technologies and unusual diseases. But topic-specific IRBs could solve this problem.

For example, under our current research oversight system, gene therapy protocols are often reviewed by local IRBs that rarely have any members who are trained in or are knowledgeable about gene therapy, nor the disease that is being studied. At the very minimum, IRBs reviewing protocols involving new technologies and/or unusual diseases, should be required to call in external experts who are knowledgeable about the technology and/or the disease that is being studied. Expertise about the basic scientific elements of a study is as essential in medicine, as it should be in research that is reviewed by members of a non-medical discipline (e.g., anthropological research being reviewed by anthropologists).

We are very concerned that your recommendations on conflict-of-interest do not go far enough. The focus seems to be on the investigators financial conflict, and not on the institutions conflict. Firstly, current FDA requirements must be changed in this regard. The FDA simply requires that an investigator must tell the sponsor if he/she has a financial conflict-of-interest, and the sponsor can keep that information secret until after the research is finished. At that time, the sponsor must tell the FDA if any of the investigators had a conflict-of-interest. Since the corporate sponsor usually pays the investigator to perform the research, there will always be a conflict-of-interest. The company must simply reveal to the FDA that it paid the investigator, or that the investigator owns stock in the company. But most importantly, this critical information does not have to be revealed to the research participant. In fact, if the research volunteer asks the FDA this question, FDA is not allowed to answer them because it is classified as "proprietary information."

We suggest that a person who volunteers to participate in a clinical trial should be told in the informed consent document if their physician owns stock in the company that is sponsoring the trial, if their doctor was paid a "finder's fee" for referring them to the trial, or if the investigator or institution holds a patent on the compound, and whether the institution where the experiment is conducted has a financial stake in the product or the company that manufactures it. If the patient knows the answers to these questions, they will be informed enough to make their own personal decision about participation in the trial.

Your recommendations about mandatory training for IRB members, and improved safety monitoring, are excellent. Data monitoring boards are a major solution to several long- standing safety problems. Creation of a *National Office of Human Research Oversight* (NOHRO) is also an excellent concept that will enable the government to respond quickly and decisively to critical research problems when they arise. We heartily endorse the NOHRO.

We also believe some of the other important contributions that this report will make is the suggestion for a national uniform system of human protections, the mandate for non-scientist members on IRBs, and most importantly, the recommendation for realistic and enforceable penalties for non-compliance, as well as requiring privately-funded research to obey national

human protection rules. These last recommendations are the missing pieces of the puzzle that have allowed the current human protection system to become non-functional.

Human research protection rules must apply to all research, not just federally-funded research. Because so much research has moved away from academia, privately-funded research is being conducted today in unregulated doctors offices and even store fronts. Thus people who volunteer for clinical trials are unaware that they are not protected by the Common Rule because no federal funds are involved. It is imperative that human protection rules are extended to all human research subjects, and we urge you to say this clearly in your report.

We also recommend that you mention in your report a need to encourage increased training of more bioethicists. In future years, there may be extreme shortages of trained personnel in this area and your report should recognize this pending need.

Again, thank you for this really excellent report and recommendations. We look forward to taking the next step toward implementation.

Very truly yours,

Abbey S. Meyers
President

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